

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) Publication number:

0 502 556 A1

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 92107178.3

(51) Int. Cl.5: A61K 9/32, A61K 9/52,
A61K 9/54

(22) Date of filing: 16.04.87

This application was filed on 28 - 04 - 1992 as a divisional application to the application mentioned under INID code 60.

(30) Priority: 30.04.86 GB 8610573

(43) Date of publication of application:
09.09.92 Bulletin 92/37

(60) Publication number of the earlier application in accordance with Art.76 EPC: 0 244 380

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(71) Applicant: Aktiebolaget Hässle
Kärragatan 5
S-431 83 Mölndal(SE)

(72) Inventor: Lövgren, Kurt
Violinvägen 2 E
S-435 00 Mölnlycke(SE)
Inventor: Pilbrant, Ake
Snödroppevägen 6
S-434 00 Kungsbacka(SE)
Inventor: Yasumura, Mitsuru
37, Matsuzono-cho 5-chome
Nishinomiya, Hyogo 662(JP)
Inventor: Morigaki, Satoshi
275-84, Nakanoma
Yachiyo-cho, Taka-gun, Hyogo 677-01(JP)
Inventor: Oda, Minoru
304-24, Ohaza-Yuya
Nakatsu-shi, Ohita 871(JP)
Inventor: Ohishi, Naohiro
1342-1, Ohaza-Tarumi, Shinyoshitomimura
Chikujo-gun, Fukuoka 871-09(JP)

(74) Representative: Linderoth, Margareta et al
AB Astra Patent Department
S-151 85 Södertälje(SE)

(54) Use of specific core material and layers to obtain pharmaceutical formulations stable to discolouration of acid labile compounds.

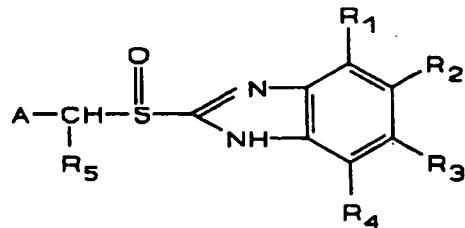
(57) The use of core material in the form of small beads or tablets containing as the active ingredient an acid labile compound of the general formula I and on said core material one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating layer, in order to obtain an oral preparation stable to discolouration.

EP 0 502 556 A1

The present invention is related to new pharmaceutical preparations containing acid labile substances for oral use and, to a method for the manufacture of such preparations.

5 Acid labile substances present a problem to the formulator when formulating a pharmaceutical dosage form for oral use. In order to prevent the substances from contact with the acid reacting gastric juice after oral intake, the conventional way to solve this problem is to coat the dosage form with an enteric coating. The coating is a group of substances/polymers with the common feature of being practically insoluble in acid media, while they are soluble in neutral to alkaline media. For substances that are labile in acid media, but have better stability in neutral to alkaline media, it is often advantageous to add alkaline reacting inactive constituents in order to increase the stability of the active compound during manufacture and 10 storage.

15 A group of compounds exerting these stability properties are substituted benzimidazoles with the general formula I



25 wherein A is an optionally substituted heterocyclic group and R¹, R², R³, and R⁴, are the same or different as defined below and R⁵ is H or a lower alkyl, or the compound 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole.

The compounds with the general formula I are virtually biologically inactive as such, but 30 degrade/transform to active inhibitors of certain enzyme systems in acid media.

As examples of compounds with the mentioned properties the compounds described in the patents US-35 A-4045 563, EP-B1-0 005 129 and BE-898 880 and the patent applications EP-A-173664, EP-A1-0 080 602, EP-0127 763, EP-0 134 400, EP-0 130 729, EP-0 150 586, DE-3415971 GB-2 082 580 and SE-A-8504048-3 may be mentioned. The last application describes 2-(2-disubstituted-aminobenzyl)sulfinyl benzimidazoles, e.g. 2- (2-dimethylaminobenzyl)sulfinyl benzimidazole, also called, NC-1300 and presented by Prof. S. Okabe at the Symposium on Drug Activity held on Oct 17th 1985 in Nagoya, Japan, and which interacts 40 with the H⁺ K⁺-ATPase after acid degradation within the parietal cells. (See for instance B. Wallmark, A. Brändström and H. Larsson "Evidence for acid-induced transformation of omeprazole into active inhibitor of H⁺ K⁺-ATPase within the parietal cell", Biochimica et Biophysica Acta 778, 549-558, 1984). Other compounds with similar properties are further mentioned in the patent US-4 182 766 and the patent applications GB-2 141 429, EP-0 146 370 and GB-2 082 580. A common feature of these compounds are that they are transformed into the biologically active compounds via rapid degradation/transformation in acid media.

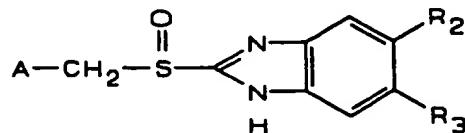
The stability profile of some compounds with the general formula I above is exemplified in the Table 1 below, where the half-life of the degradation/transformation reaction in solution at pH 2 and 7 are given.

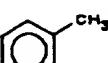
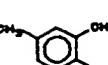
45

50

55

Table 1. Rate of degradation/transformation of compounds with the general structure



15 20 25 30 35 40 45	Compound No	Half-life (minutes for the trans- formation to the active moiety)			
		A	R ²	R ³	at pH=2
1. 5-COOCH ₃ ; 6-CH ₃					11 150
					
2. 5-CH ₃ ; H					5.4 1700
					
3. 5-CF ₃ ; H					1.9 122
					

Cont.

5	Compound	Half-life (minutes for the trans-			
	No	formation to the active moiety			
10	A	R ²	R ³	at pH=2	at pH=7
15	4. 5-CF ₃ ;H			2.0	8.8
20	5. 5-OCH ₃ ;H			3.7	1620
25	6. 5-OCH ₃ ;H			4.0	3900
30	7. 5-C ₂ H ₅ ;H			33	not determined
40					
45					

50 Substituted sulfoxides, such as, for instance, the substituted benzimidazoles described in EP-B1-0005129 are potent inhibitors of gastric acid secretion. The substituted benzimidazoles are susceptible to degradation/transformation in acid reacting and neutral media.

55 It is an inherent property of these compounds to be activated to the active moiety in the acid environment within the parietal cells. The activated compound interacts with the enzyme in the parietal cells, which mediates the production of hydrochloric acid in the gastric mucosa. All compounds of the class of substituted benzimidazoles, containing a sulfoxide grouping, which interferes with the H⁺K⁺-ATPase in the parietal cells hitherto known are all also degraded in acid media.

A pharmaceutical dosage form of acid labile substances, which prevents the substances from contact

with acidic gastric juice, must be enteric coated. Ordinary enteric coatings, however, are made of acidic compounds. If covered with such a conventional enteric coating, the acid labile substance rapidly decomposes by direct or indirect contact with it, with the result that the preparations become badly discoloured and lose in content of the active compound with the passage of time.

5 In order to enhance the storage stability, the cores which contain the acid labile substance must also contain alkaline reacting constituents. When such an alkaline core is enteric coated with an amount of a conventional enteric coating polymer such as, for example, cellulose acetate phthalate, that permits the dissolution of the coating and the active drug contained in the cores in the proximal part of the small intestine, it also will allow some diffusion of water or gastric juice through the enteric coating into the cores, 10 during the time the dosage form resides in the stomach before it is emptied into the small intestine. The diffused water of gastric juice will dissolve parts of the core in the close proximity of the enteric coating layer and there form an alkaline solution inside the coated dosage form. The alkaline solution will interfere with the enteric coating and eventually dissolve it.

In DE-A1-3 046 559 a way to coat a dosage form is described. First the dosage form is coated with a 15 water insoluble layer containing microcrystalline cellulose and then with a second enteric coating with the aim to achieve a dosage form which releases the active drug in the colon. This method of preparation will not give the desired release of the compounds with the general formula I above in the small intestine.

US-A-2 540 979 describes an enteric coated oral dosage form, where the enteric coating is combined with a second and/or first coating of a water insoluble "wax" layer. This method of preparation is not 20 applicable on cores containing a compound with the general formula I since direct contact between substances such as cellulose acetate phthalate (CAP) and a compound of formula I causes degradation and discolouration of the compounds of the formula I.

DE-B2-23 36 218 describes a method to produce a dialysis membrane consisting of a mixture of one or 25 more conventional enteric coating polymers and one or more insoluble cellulose derivates. Such a membrane will not give a proper protection of the acid labile compounds of the formula I in gastric juice.

DE-A1-1 204 363 describes a three-layer coating procedure. The first layer is soluble in gastric but is 30 insoluble in intestinal juice. The second is water soluble regardless of pH and the third layer is an enteric coating. This preparation as well as the preparation described in DE-A1-1 617 615 result in a dosage form which is not dissolved in gastric juice and which only dissolves slowly in intestinal juice. Such preparations 35 cannot be used for the compounds of the formula I, where a rapid release of the drug in the small intestine is needed. DE-A1 12 04 363 describes coating with three layers to achieve release of a drug in the ileum, an aim which is outside the scope of the present invention. GB-A-1 485 676 describes a way to obtain a preparation which effervesces in the small intestine. This is obtained by the enteric coating of a core containing the active drug and an effervescing system such as a combination of carbonate and/or 40 bicarbonate salt and a pharmaceutically acceptable acid. This formulation cannot be adopted for a pharmaceutical dosage form containing a compound of formula I as the presence of an acid in contact with a compound of formula I in the cores would give as a result that the compound of formula I was degraded.

WO 85/03436 describes a pharmaceutical preparation wherein cores containing active drugs mixed with, for instance, buffering components such as sodium dihydrogenphosphate with the aim of maintaining a 45 constant pH and a constant rate of diffusion, are coated with a first coating which controls the diffusion. This formulation cannot be adopted for acid labile compounds where a rapid release in the small intestine is wanted. Direct application of an enteric coating onto the cores would also adversely influence the storage stability of such dosage forms containing acid labile compounds.

EP-A-124 495 and EP-A-173 664 describe enteric coated granules without subcoating or a powder that 45 are filled into hard gelatine capsules or a solution that is filled into a soft capsule.

The object of the present invention is to provide an oral, pharmaceutical preparation stable to discolouration containing an acid labile compound of the general formula I above wherein A is an optionally substituted heterocyclic group, R¹, R², R³, and R⁴, are the same or different and preferably hydrogen, lower alkyl, lower alkoxy, -CF₃,

50

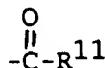


55 or halogen and R⁵ is H or lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole; or the acidic labile compound is 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole as the active ingredient. The core material is in the form of small beads or tablets containing the active ingredient

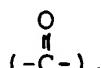
together with an alkaline reacting compound, or an alkaline salt of the active ingredient optionally together with an alkaline reacting compound, and on said core material one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating.

5 R¹, R², R³ and R⁴, which are the same or different and especially

- (a) hydrogen
- (b) halogen, e.g. F, Cl, Br, I
- (c) -CN
- 10 (d) -CHO
- (e) -CF₃
- (f)



(g) -O-C-R¹²
 (h) -CH(OR¹³)₂
 20 (i) -(Z)_n-B-D
 (j) aryl containing up to 10 carbon atoms
 (k) aryloxy containing up to 10 carbon atoms, optionally substituted by alkyl containing 1-6 carbon atoms
 (l) -alkylthio containing 1-6 carbon atoms
 (m) -NO₂
 25 (n) -alkylsulfinyl containing 1-6 carbon atoms
 (o) or wherein adjacent groups R¹, R², R³ and R⁴ together with the adjacent carbon atoms in the benzimidazole ring form a 5-, 6- or 7-membered monocyclic ring or a 9-, 10- or 11-membered bicyclic ring, which rings may be saturated or unsaturated and may contain 0-3 hetero atoms selected from -N- and -O-, and which rings may be optionally substituted with 1-4 substituents selected from alkyl groups with 1-3 carbon atoms, alkylene radicals containing 4-5 carbon atoms giving spiro compounds, or two or 30 four of these substituents together form one or two oxo groups



whereby if R¹ and R², R² and R³ or R³ and R⁴ together with the adjacent carbon atoms in the benzimidazole ring form two rings they may be condensed with each other, in which formulas R¹¹ and R¹², which are the same or different, are

40 (a) aryl containing up to 10 carbon atoms
 (b) alkoxyalkoxy containing 1-4 carbon atoms
 (c) alkoxy containing 1-3 carbon atoms in each alkoxy part
 (d) arylalkoxy containing 1-2 carbon atoms in the alkoxy part and up to 10 carbon atoms in the aryl part
 45 (e) aryloxy containing up to 10 carbon atoms
 (f) dialkylamino containing 1-3 carbon atoms in the alkyl parts, or
 (g) pyrrolidino or piperidino, optionally substituted with alkyl containing 1-3 carbon atoms;

R¹³ is

50 (a) alkyl containing 1-4 carbon atoms, or
 (b) alkylene containing 2-3 carbon atoms;

Z is -O- or



n is 0 or 1;

B is

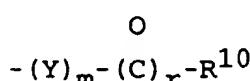
5 (a) alkylene containing 1-6 carbon atoms
 (b) cycloalkylene containing 3-6 carbon atoms
 (c) alkynylene containing 2-6 carbon atoms
 (d) cycloalkynylene containing 3-6 carbon atoms, or
 (e) alkynylene containing 2-6 carbon atoms;

D is

10 (a) H
 (b) -CN
 (c)



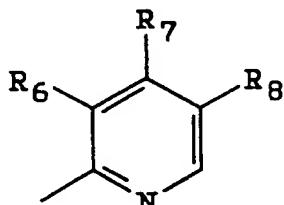
(d)

wherein
R⁹ is

25 (a) alkoxy containing 1-5 carbon atoms, or
 (b) dialkylamino containing 1-3 carbon atoms in the alkyl parts;

m is 0 or 1;
r is 0 or 1;30 Y is
 (a) -O-
 (b) -NH-
 (c) -NR¹⁰-;R¹⁰ is

35 (a) H
 (b) alkyl containing 1-3 carbon atoms
 (c) arylalkyl containing 1-2 carbon atoms in the alkyl part and up to 10 carbon atoms in the aryl part
 (d) aryl containing up to 10 carbon atoms;

40 R⁵ is H, CH₃ or C₂H₅;A is especially a pyridyl group in which R⁶ and R⁸ are the same or different, are

50

(a) H or
 (b) alkyl containing 1-6 carbon atoms;

R⁷ is

55 (a) H
 (b) alkyl containing 1-8 carbon atoms
 (c) alkoxy containing 1-8 carbon atoms
 (d) alkenyloxy containing 2-5 carbon atoms

(e) alkynyoxy containing 2-5 carbon atoms
 (f) alkoxyalkoxy containing 1-2 carbon atoms in each alkoxy group
 (g) aryl containing up to 10 carbon atoms
 5 (f) arylalkyl containing 1-6 carbon atoms in the alkyl part and up to 10 carbon atoms in the aryl part
 (i) aryloxy containing up to 10 carbon atoms, optionally substituted by alkyl containing 1-6 carbon atoms
 (j) arylalkoxy containing 1-6 carbon atoms in the alkoxy part and up to 10 carbon atoms in the aryl part
 10 (k) dialkylaminoalkoxy containing 1-2 carbon atoms in the alkyl substituents on the amino nitrogen and 1-4 carbon atoms in the alkoxy group
 (l) oxacycloalkyl containing one oxygen atom and 3-7 carbon atoms
 (m) oxacycloalkoxy containing two oxygen atoms and 4-7 carbon atoms
 (n) oxacycloalkylalkyl containing one oxygen atom and 4-7 carbon atoms
 15 (o) oxacycloalkylalkoxy containing two oxygen atoms and 4-6 carbon atoms, or
 (p) R⁶ and R⁷, or R⁷ and R⁸ together with the adjacent carbon atoms in the pyridine ring form a ring wherein the part constituted by R⁶ and R⁷, or R⁷ and R⁸, is

-CH = CH-CH = CH-

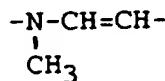
20 -O-(CH₂)_p-

-S-(CH₂)_v-

-CH₂(CH₂)_p-

-O-CH = CH-

-NH-CH = CH-



30 wherein p is 2, 3 or 4, v is 2 or 3 and the O and N atoms always are attached to position 4 in the pyridine ring; provided that not more than one of R⁶, R⁷ and R⁸ is hydrogen can be formulated into an enteric coated dosage form.

The object of the present invention is thus an enteric coated dosage form of acid labile compounds with the general formula I defined above except the compound omeprazole, 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole. Another compound, which may be enteric coated according to the invention is 2-[(2-dimethyl-aminobenzyl)sulfinyl]-benzimidazole. The new preparations are resistant to dissolution in acid media, dissolve rapidly in neutral to alkaline media and have a good stability during long-term storage. The new dosage form is characterized in the following way. Cores containing the acid labile compound mixed with alkaline compounds or an alkaline salt of the acid labile compound optionally mixed with an alkaline compound are coated with two or more layers, whereby the first layer/layers is/are soluble in water or rapidly disintegrating in water and consist(s) of non-acidic, otherwise inert pharmaceutically acceptable substances. This/these first layer/layers separates/separate the alkaline core material from the outer layer, which is an enteric coating. The final, enteric coated dosage form is treated in a suitable way to reduce the water content to a very low level in order to obtain a good stability with virtually no discolouration of the dosage form during long-term storage.

As examples of compounds especially suitable for the pharmaceutical dosage form according to the invention the compounds listed in Table 1 can be mentioned.

The half-life of degradation of the compounds 1-6 in Table 1 in water solution at pH-values less than 50 four is in most cases shorter than ten minutes. Also at neutral pH-values the degradation reaction proceeds rapidly, e.g. at pH=7 the half-life of degradation is between 10 minutes and 65 hours while at higher pH-values the stability in solution for most compounds is much better. The stability profile is similar in solid phase. The degradation is catalyzed by acid reacting substances. The acid labile compounds are stabilized in mixtures with alkaline reacting substances.

55 From what is said about the stability properties of the acid labile compounds listed above it is obvious that an oral dosage form of the said compounds must be protected from contact with the acid reacting gastric juice in order to reach the small intestine without degradation.

Cores

The acid labile compound is mixed with inert, preferably water soluble, conventional pharmaceutical constituents to obtain the preferred concentration of the active compound in the final mixture and with an alkaline reacting, otherwise inert, pharmaceutically acceptable substance (or substances), which creates a "micro-pH" around each particle of active compound of not less than pH = 7, preferably not less than pH = 8, when water is adsorbed to the particles of the mixture or when water is added in small amounts to the mixture. Such substances can be chosen among substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane or other similar, pharmaceutically acceptable pH-buffering substances. The stabilizing, high pH-value in the powder mixture can also be achieved by using an alkaline reacting salt of the active compound such as the sodium, potassium, magnesium, calcium salts of acid labile compounds, either alone or in combination with a conventional buffering substance as previously described.

The powder mixture is then formulated into small beads i.e. pellets, or tablets, by conventional pharmaceutical procedures. The pellets or tablets are used as cores for further processing.

20

Separating layer

The alkaline reacting cores containing an acid labile compound must be separated from the enteric coating polymer(s) containing free carboxyl groups, which otherwise causes degradation/discolouration of the acid labile compound during the coating process or during storage. The subcoating layer, (the separating layer), also serves as a pH-buffering zone in which hydrogen ions diffusing from the outside in towards the alkaline core towards the surface of the coated articles. The pH-buffering properties of the separating layer can be further strengthened by introducing in the layer substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$, wherein n not is an integer and less than 2 or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, citric or other suitable, weak, inorganic or organic acids.

35 The separating layer consists of one or more water soluble inert layer, optionally containing pH-buffering compounds.

The separating layer(s) can be applied to the cores - pellets or tablets - by conventional coating procedures in a suitable coating pan or in a fluidized bed apparatus using water and/or conventional organic solvents for the coating solution. The material for the separating layer is chosen among the pharmaceutically acceptable, water soluble, inert compounds or polymers used for film-coating applications such as, for instance, sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, hydroxypropyl cellulose, hydroxymethyl cellulose or hydroxypropyl methylcellulose. The thickness of the separating layer is not less than 2 μm , for small spherical pellets preferably not less than 4 μm , for tablets preferably not less than 10 μm .

45 In the case of tablets another method to apply the coating can be performed by the drycoating technique. First a tablet containing the acid labile compound is compressed as described above. Around this tablet a layer is compressed using a suitable tabletting machine. The outer, separating layer, consists of pharmaceutically acceptable, in water soluble or in water rapidly disintegrating tablet excipients. The separating layer has a thickness of not less than 1 mm. Ordinary plasticizers colorants, pigments, titanium dioxide, talc and other additives may also be included into the separating layer.

55 The enteric layer coating layer is applied on to the subcoated cores by conventional coating techniques such as, for instance, pan coating or fluidized bed coating using solutions or polymers in water and/or suitable organic solvents or by using latex suspensions of said polymers. As enteric coating polymers can be used, for example, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl esters such as, for instance, compounds known under the trade name Eudragit \circledR L 12,5 or Eudragit \circledR L 100 (Röhm Pharma), or similar compounds used to obtain enteric coatings.

The enteric coating can also be applied using water-based polymer dispersions, e.g. Aquateric \circledR (FMC

Corporation), Eudragit® L100-55 (Röhm Pharma), Coating CE 5142 (BASF). The enteric coating layer can optionally contain a pharmaceutically acceptable plasticizer such as, for instance, cetanol, triacetin, citric acid esters such as, for instance, those known under the trade name Citroflex® (Pfizer), phthalic acid esters, dibutyl succinate or similar plasticizers.

5 The amount of plasticizer is usually optimized for each enteric coating polymer(s) and is usually in the range of 1-20% of the enteric coating polymer(s). Dispersants such as talc, colourants and pigments may also be included into the enteric coating layer.

Thus, the special preparation according to the invention consists of cores containing the acid labile compound mixed with an alkaline reacting compound or cores containing an alkaline salt of the acid labile 10 compound optionally mixed with an alkaline reacting compound. The cores suspended in water forms a solution or a suspension which has a pH, which is higher than that of a solution in which the polymer used for enteric coating is just soluble. The cores are coated with a water soluble or in water rapidly 15 disintegrating coating, optionally containing a pH-buffering substance, which separates the alkaline cores from the enteric coating. Without this separating layer the resistance towards gastric juice would be too short and the storage stability of the dosage form would be unacceptably short. The sub-coated dosage form is finally coated with an enteric coating rendering the dosage form insoluble in acid media, but rapidly 20 disintegrating/dissolving in neutral to alkaline media such as, for instance, the liquids present in the proximal part of the small intestine, the site where dissolution is wanted.

20 Final dosage form

The final dosage form is either an enteric coated tablet or capsule or in the case of enteric coated pellets, pellets dispensed in hard gelatin capsules or sachets or pellets formulated into tablets. It is essential 25 for the long term stability during storage that the water content of the final dosage form containing acid labile compound (enteric coated tablets, capsules or pellets) is kept low, preferably not exceeding 1.5 % by weight.

A process for the manufacture of the oral dosage form represents a further aspect of the invention. After the forming of the cores the cores are first coated with the separating layer and then with the enteric coating layer. The coating is carried out as described above.

30 The preparation according to the invention is especially advantageous in reducing gastric acid secretion and/or providing a gastrointestinal cytoprotective effect. It is administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general the dosage will be in the 35 range of 1 to 400 mg per day of active substance. A method for the treatment of such conditions using the novel oral dosage form represents a further aspect of the invention.

The invention is described in detail in the following examples:

EXAMPLES

40 Examples 1-3 exemplify the invention.

Example 1

Uncoated pellets

45

50

55

5	I	Lactose powder	253 g
		Lactose anhydrous	167 g
		Hydroxypropyl cellulose	25 g
10	II	Compound 1, Table 1	50 g
		Sodium lauryl sulphate	5 g
		Disodium hydrogen phosphate	1.5 g
		Sodium dihydrogen phosphate	0.1 g
15		Distilled water	125 g

20 The dry ingredients (I) were premixed in a mixer. Addition of a granulation liquid (II) containing the suspended active compound was made and the mass was wet-mixed to a proper consistency. The wet mass was pressed through an extruder and spheronized to pellets. The pellets were dried and classified into suitable particle size ranges.

Subcoated pellets

25	III	Uncoated pellets	500 g
		Hydroxypropyl methyl-	
		cellulose	20 g
30		Distilled water	400 g

35 The polymer solution (III) was sprayed onto the uncoated pellets in a fluidized bed apparatus. The spray guns were placed above the fluidized bed.

Enteric coated pellets

40	IV	Subcoated pellets	500 g
		Hydroxypropyl methylcellulose	
		phthalate	57 g
		Cetyl alcohol	3 g
45		Acetone	540 g
		Ethanol	231 g

50 The polymer solution (IV) was sprayed on the subcoated pellets in a fluidized bed apparatus with spray guns placed above the bed. After drying to a water content of 0.5 % the enteric coated pellets were classified and filled into hard gelatin capsules in an amount of 284 mg, corresponding to 25 mg of active compound 1. 30 capsules were packed in tight containers together with a desiccant.

Example 2

Formulation with the sodium salt of compound 2 according to Table 1.

Uncoated pellets

5	I	Compound 2, Table 1 sodium salt	339	g
10		Mannitol powder	2 422	g
15		Lactose anhydrous	120	g
20		Hydroxypropyl cellulose	90	g
25	II	Microcrystalline cellulose	60	g
30		Sodium lauryl sulphate	7	g
35		Distilled water	650	g

The preparation was made as described in Example 1 with the exception that the sodium salt of compound 2 was added together with the other ingredients in mixture 1.

Subcoated pellets

25	III	Uncoated pellets	500	g
30		Hydroxypropyl methylcellulose	20	g
35		Aluminium hydroxide/magnesium carbonate	4	g
40		Distilled water	400	g
45		Pellets subcoated with III	500	g
50	IV	Hydroxypropyl methylcellulose	20	g
55		Distilled water	400	g

The two subcoat layers, III and IV, were applied to the uncoated pellets in a fluidized bed apparatus in consecutive order as previously described.

Enteric coated pellets

45	V	Subcoated pellets	500	g
50		Hydroxypropyl methylcellulose	57	g
55		phthalate	3	g
60		Cetyl alcohol	540	g
65		Acetone	231	g
70		Ethanol		

The preparation of enteric coated pellets was performed as described in Example 1.

Example 3

5 Formulation with compound 6, according to Table 1. This example gives the composition of one unit dose according to the invention.

Tablet core

10

Compound 6, Table 1	15 mg
Lactose	119 mg
Hydroxypropyl cellulose (low substitution)	5 mg
Hydroxypropyl cellulose	1 mg
Talc	5 mg
Mg(OH) ₂	15 mg
TOTAL	160 mg

15

20 Tablet cores having the composition above and each weighing 160 mg were first made by known techniques.

Separating layer (inner)

25

Hydroxypropyl cellulose	2 mg
Synthetic hydrotalcite [Al ₂ O ₃ · 6MgO · CO ₂ · 12H ₂ O]	0.3 mg

30

Separating layer (outer)

35

Hydroxypropyl cellulose	2 mg
-------------------------	------

The two separating layers were applied to the cores by known coating techniques.

Enteric coating layer

40

Hydroxypropyl methylcellulose phthalate	7 mg
Cetyl alcohol	0.5 mg

45

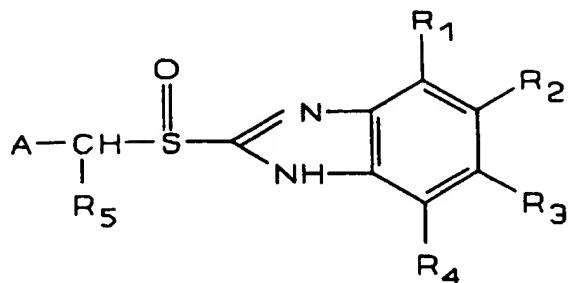
The enteric coating solution was sprayed on the cores coated by the two separating layers by known enteric coating techniques.

Claims

50

1. The use of core material in the form of small beads or tablets containing as the active ingredient an acid labile compound of the general formula I

55



wherein A is an optionally substituted heterocyclic group, R¹, R², R³ and R⁴ are the same or different and preferably hydrogen,

15 lower alkyl, lower alkoxy, -CF₃,



or halogen and R⁵ is H or a lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole; or the acid labile compound is 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole together with an alkaline reacting compound, or an alkaline salt of the active ingredient optionally together with an alkaline reacting compound, and on said core material one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating, in order to obtain an oral pharmaceutical preparation of said acid labile compound which is stable to discolouration.

2. The use according to claim 1 wherein the subcoating comprises hydroxypropyl methylcellulose, hydroxypropyl cellulose or polyvinylpyrrolidone.
3. The use according to claim 1 wherein the subcoating comprises two or more sub-layers and where the inner layer comprises one or more of magnesium oxide, magnesium hydroxide or composite substance Al₂O₃.6MgO₂O or MgO.Al₂O₃.2SiO₂.nH₂O, wherein n is an integer and less than two.
4. The use according to claim 1 wherein the alkaline core comprises the acid labile compound and pH-buffering alkaline compound rendering to the microenvironment of the acid labile compound a pH of 7-12.
5. The use according to claim 4 wherein the alkaline compound comprises one or more of magnesium oxide, hydroxide or carbonate, aluminium hydroxide, aluminium, calcium, sodium or potassium carbonate, phosphate or citrate, the composite aluminium/magnesium compounds Al₂O₃.6MgO₂.CO₂.12H₂O or MgO.Al₂O₃.2SiO₂.nH₂O, wherein n is not an integer and less than two.
6. The use according to claim 1 wherein the alkaline core comprises an alkaline salt of the acid labile compound such as the sodium, potassium, magnesium, calcium or ammonium salt.
7. The use according to claim 5 wherein the alkaline core comprises an alkaline salt of the acid labile compound mixed with an inert, alkaline compound.
8. The use according to claim 1 wherein the enteric coating comprises hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl ester or polyvinyl acetate phthalate, optionally containing a plasticizer.
9. The use according to claim 1 wherein the water content of the final dosage form containing the acid

EP 0 502 556 A1

labile compound does not exceed 1.5 % by weight.

5

10

15

20

25

30

35

40

45

50

55



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 10 7178
Page 1

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D, X	EP-A-0 173 664 (AKTIEBOLAGET HÄSSLE) * page 2, line 1 - page 3, line 26 * * page 21, line 26 - page 22, line 8 * * page 27, line 1 - line 20 * * page 37, line 19 - page 38, line 12 * ---	1,4-9	A61K9/32 A61K9/52 A61K9/54
Y	FR-A-2 272 639 (A. WARREN ET AL.) * page 1, line 1 - line 3 * * page 2, line 19 - page 3, line 20 * ---	2,3	
D, A	EP-A-0 080 602 (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) * page 2, line 1 - line 21 * * page 3, line 6 - line 13 * * page 17, line 10 - line 20 * * page 18, line 1 - line 20 * * page 20, line 4 - line 22 * ---	1-9	
A	GB-A-760 403 (ABBOT LABORATORIES) * page 1, line 11 - line 34 * * page 2, line 31 - line 70 * * page 6, line 3 - line 18 * ---	1-9	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
A	DE-A-3 233 764 (R.P. SCHERER GMBH) * page 6, line 7 - page 7, paragraph 3 * * page 8, last paragraph - page 9, line 1 * ---	1-9	
A	PATENT ABSTRACTS OF JAPAN vol. 8, no. 106 (C-223)(1543) 18 May 1984 & JP-A-59 020 219 (SHINETSU KAGAKU KOGYO K. K.) 1 February 1984 * abstract * ---	1-9	A61K
E	EP-A-0 446 961 (TAKEDA CHEMICAL INDUSTRIES LTD.) 18 September 1991 * page 2 - page 3, line 6 * * page 7, line 50 - page 8, line 11 * * page 8, line 25 - line 32 * * examples 7,9 * * claims 12,20-27 *	1-9	
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	13 JULY 1992	MUELLNERS W.	
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone	T : theory or principle underlying the invention		
Y : particularly relevant if combined with another document of the same category	E : earlier patent document, but published on, or after the filing date		
A : technological background	D : document cited in the application		
O : non-written disclosure	L : document cited for other reasons		
P : intermediate document	A : member of the same patent family, corresponding document		



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 10 7178
Page 2

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
E	EP-A-0 423 748 (TAKEDA CHEMICAL INDUSTRIES LTD.) 24 April 1991 * claims 11,19--31 *	1-9	
E	EP-A-0 237 200 (TAKEDA CHEMICAL INDUSTRIES LTD.) 16 September 1987 * claims 1,9,10 *	1-9	
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
<p>The present search report has been drawn up for all claims</p>			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	13 JULY 1992	MUELLNERS W.	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons A : member of the same patent family, corresponding document X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document	



(19)

Europäisches Patentamt

European Patent Office

Office européen des brevets



(11)

EP 0 502 556 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention
of the grant of the patent:
26.06.1996 Bulletin 1996/26

(51) Int. Cl.⁶: A61K 9/32, A61K 9/52,
A61K 9/54

(21) Application number: 92107178.3

(22) Date of filing: 16.04.1987

(54) Use of specific core material and layers to obtain pharmaceutical formulations stable to
discolouration of acid labile compounds

Verwendung von spezifischem Kernmaterial und Schichten zur Herstellung pharmazeutischer
Formulierungen, die stabil gegen die Verfärbung säurelabiler Verbindungen sind

Utilisation d'un matériau à noyau et de couches pour obtenir des formulations pharmaceutiques stable
au changement de couleur des composés sensibles aux acides

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

• Yasumura, Mitsuru
Nishinomiya, Hyogo 662 (JP)
• Morigaki, Satoshi
Yachiyo-cho, Taka-gun, Hyogo 677-01 (JP)
• Oda, Minoru
Nakatsu-shi, Ohita 871 (JP)
• Ohishi, Naohiro
Chikujo-gun, Fukuoka 871-09 (JP)

(30) Priority: 30.04.1986 GB 8610573

(74) Representative: Linderoth, Margareta et al
AB Astra
Patent Department
151 85 Södertälje (SE)

(43) Date of publication of application:
09.09.1992 Bulletin 1992/37

(56) References cited:

(62) Application number of the earlier application in
accordance with Art. 76 EPC: 87850126.1

EP-A- 0 080 602	EP-A- 0 173 664
EP-A- 0 237 200	EP-A- 0 423 748
EP-A- 0 446 961	DE-A- 3 233 764
FR-A- 2 272 639	GB-A- 760 403

• PATENT ABSTRACTS OF JAPAN vol. 8, no. 106
(C-223)(1543) 18 May 1984

(60) Divisional application: 93201612.4

(73) Proprietor: Aktiebolaget Hässle
S-431 83 Mölndal (SE)

(72) Inventors:

• Lövgren, Kurt
S-435 00 Mölndal (SE)
• Pilbrant, Ake
S-434 00 Kungsbacka (SE)

EP 0 502 556 B1

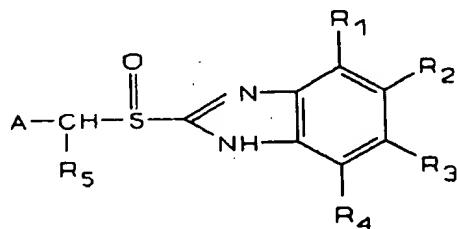
Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give
notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in
a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art.
99(1) European Patent Convention).

Description

The present invention is related to new pharmaceutical preparations containing acid labile substances for oral use, which pharmaceutical preparations are stable to discolouration, and to a method for the manufacture of such preparations.

5 Acid labile substances present a problem to the formulator when formulating a pharmaceutical dosage form for oral use. In order to prevent the substances from contact with the acid reacting gastric juice after oral intake, the conventional way to solve this problem is to coat the dosage form with an enteric coating. The coating is a group of substances/polymers with the common feature of being practically insoluble in acid media, while they are soluble in neutral to alkaline media. For substances that are labile in acid media, but have better stability in neutral to alkaline media, it is often 10 advantageous to add alkaline reacting inactive constituents in order to increase the stability of the active compound during manufacture and storage.

15 A group of compounds exerting these stability properties are substituted benzimidazoles with the general formula I



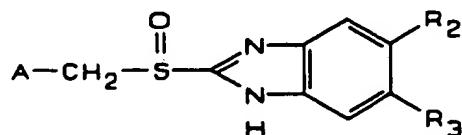
wherein A is an optionally substituted heterocyclic group and R₁, R₂, R₃, and R₄, are the same or different as defined below and R₅ is H or a lower alkyl, or the compound 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole.

30 The compounds with the general formula I are virtually biologically inactive as such, but degrade/transform to active inhibitors of certain enzyme systems in acid media.

35 As examples of compounds with the mentioned properties the compounds described in the patents US-A-4045 563, EP-B1-0 005 129 and BE-898 880 and the patent applications EP-A-173664, EP-A1-0 080 602, EP-0127 763, EP-0 134 400, EP-0 130 729, EP-0 150 586, DE-3415971 GB-2 082 580 and SE-A-8504048-3 may be mentioned. The last application describes 2-(2-disubstituted-aminobenzyl)sulfinyl benzimidazoles, e.g. 2- (2-dimethylaminobenzyl)sulfinyl benzimidazole, also called, NC-1300 and presented by Prof. S. Okabe at the Symposium on Drug Activity held on Oct 17th 1985 in Nagoya, Japan, and which interacts with the H⁺K⁺-ATPase after acid degradation within the parietal cells. (See for instance B. Wallmark, A. Brändström and H. Larsson "Evidence for acid-induced transformation of omeprazole into active inhibitor of H⁺K⁺-ATPase within the parietal cell", Biochimica et Biophysica Acta 778, 549-558, 1984). Other compounds with similar properties are further mentioned in the patent US-4 182 766 and the patent applications GB-2 141 429, EP-0 146 370 and GB-2 082 580. A common feature of these compounds are that they are transformed into the biologically active compounds via rapid degradation/transformation in acid media.

40 The stability profile of some compounds with the general formula I above is exemplified in the Table 1 below, where the half-life of the degradation/transformation reaction in solution at pH 2 and 7 are given.

5
Table 1. Rate of degradation/transformation of
compounds with the general structure



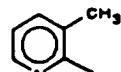
15

Compound	Half-life (minutes for the trans-		
No	formation to the active moiety		
	A	R ²	R ³
		at pH=2	at pH=7

20

1. 5-COOCH ₃ ; 6-CH ₃	11	150
---	----	-----

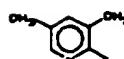
25



30

2. 5-CH ₃ ; H	5.4	1700
--------------------------	-----	------

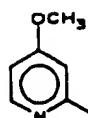
35



40

3. 5-CF ₃ ; H	1.9	122
--------------------------	-----	-----

45



50

Cont.

55

5	Compound No	Half-life (minutes for the trans- formation to the active moiety)			
		A	R ²	R ³	at pH=2
10	4. 5-CF ₃ ;H				2.0 8.8
15					
20	5. 5-OCH ₃ ;H				3.7 1620
25					
30	6. 5-OCH ₃ ;H				4.0 3900
35					
40	7. 5-C ₂ H ₅ ;H				33 not determined
45					

50 Substituted sulfoxides, such as, for instance, the substituted benzimidazoles described in EP-B1-0005129 are potent inhibitors of gastric acid secretion. The substituted benzimidazoles are susceptible to degradation/transformation in acid reacting and neutral media.

55 It is an inherent property of these compounds to be activated to the active moiety in the acid environment within the parietal cells. The activated compound interacts with the enzyme in the parietal cells, which mediates the production of hydrochloric acid in the gastric mucosa. All compounds of the class of substituted benzimidazoles, containing a sulfoxide grouping, which interferes with the H⁺K⁺-ATPase in the parietal cells hitherto known are all also degraded in acid media.

5 A pharmaceutical dosage form of acid labile substances, which prevents the substances from contact with acidic gastric juice, must be enteric coated. Ordinary enteric coatings, however, are made of acidic compounds. If covered with such a conventional enteric coating, the acid labile substance rapidly decomposes by direct or indirect contact with it, with the result that the preparations become badly discoloured and lose in content of the active compound with the passage of time.

10 In order to enhance the storage stability, the cores which contain the acid labile substance must also contain alkaline reacting constituents. When such an alkaline core is enteric coated with an amount of a conventional enteric coating polymer such as, for example, cellulose acetate phthalate, that permits the dissolution of the coating and the active drug contained in the cores in the proximal part of the small intestine, it also will allow some diffusion of water or gastric juice through the enteric coating into the cores, during the time the dosage form resides in the stomach before it is emptied into the small intestine. The diffused water or gastric juice will dissolve parts of the core in the close proximity of the enteric coating layer and there form an alkaline solution inside the coated dosage form. The alkaline solution will interfere with the enteric coating and eventually dissolve it.

15 In DE-A1-3 046 559 a way to coat a dosage form is described. First the dosage form is coated with a water insoluble layer containing microcrystalline cellulose and then with a second enteric coating with the aim to achieve a dosage form which releases the active drug in the colon. This method of preparation will not give the desired release of the compounds with the general formula I above in the small intestine.

20 US-A-2 540 979 describes an enteric coated oral dosage form, where the enteric coating is combined with a second and/or first coating of a water insoluble "wax" layer. This method of preparation is not applicable on cores containing a compound with the general formula I since direct contact between substances such as cellulose acetate phthalate (CAP) and a compound of formula I causes degradation and discolouration of the compounds of the formula I.

25 DE-B2-23 36 218 describes a method to produce a dialysis membrane consisting of a mixture of one or more conventional enteric coating polymers and one or more insoluble cellulose derivates. Such a membrane will not give a proper protection of the acid labile compounds of the formula I in gastric juice.

30 DE-A1-1 204 363 describes a three-layer coating procedure. The first layer is soluble in gastric but is insoluble in intestinal juice. The second is water soluble regardless of pH and the third layer is an enteric coating. This preparation as well as the preparation described in DE-A1-1 617 615 result in a dosage form which is not dissolved in gastric juice and which only dissolves slowly in intestinal juice. Such preparations cannot be used for the compounds of the formula I, where a rapid release of the drug in the small intestine is needed. DE-A1 12 04 363 describes coating with three layers to achieve release of a drug in the ileum, an aim which is outside the scope of the present invention. GB-A-1 485 676 describes a way to obtain a preparation which effervesces in the small intestine. This is obtained by the enteric coating of a core containing the active drug and an effervesing system such as a combination of carbonate and/or bicarbonate salt and a pharmaceutically acceptable acid. This formulation cannot be adopted for a pharmaceutical dosage form containing a compound of formula I as the presence of an acid in contact with a compound of formula I in the cores would give as a result that the compound of formula I was degraded.

35 WO 85/03436 describes a pharmaceutical preparation wherein cores containing active drugs mixed with, for instance, buffering components such as sodium dihydrogenphosphate with the aim of maintaining a constant pH and a constant rate of diffusion, are coated with a first coating which controls the diffusion. This formulation cannot be adopted for acid labile compounds where a rapid release in the small intestine is wanted. Direct application of an enteric coating onto the cores would also adversely influence the storage stability of such dosage forms containing acid labile compounds.

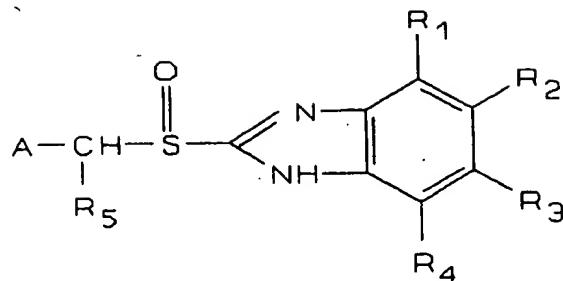
40 EP-A-124 495 and EP-A-173 664 describe enteric coated granules without subcoating or a powder that are filled into hard gelatine capsules or a solution that is filled into a soft capsule.

45 The object of the present invention is to provide an oral, pharmaceutical preparation stable to discolouration comprising (i) an alkaline reacting core material containing as the active ingredient an acid labile compound of the general formula I above wherein A, R¹, R², R³, R⁴, and R⁵ and the acid labile compound are as defined below, together with an alkaline reacting compound, or an alkaline salt of the active ingredient optionally together with an alkaline reacting compound, and (ii) an outer layer, which is an enteric coating.

50 This object is achieved in the use of a specific subcoating in the oral pharmaceutical preparation.

55 The present invention therefore provides the use of a subcoating which is comprised of one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water or polymeric, water-soluble, film-forming compounds, optionally containing pH-buffering alkaline compounds, in order to obtain stability to discolouration in an oral pharmaceutical formulation comprising an alkaline reacting core material containing as the active ingredient (i) a compound of the formula I

5

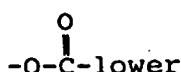


10

15

wherein A is an optionally substituted heterocyclic group, R₁, R₂, R₃ and R₄ are the same or different and are hydrogen, lower alkyl, lower alkoxy, CF₃.

20



25

alkyl or halogen and R⁵ is H or a lower alkyl group wherein "lower" denotes 1-6 carbon atoms, except the compound omeprazole, together with an alkaline reacting compound, or 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole together with an alkaline reacting compound or (ii) an alkaline salt of a compound of formula I optionally together with an alkaline reacting compound, or an alkaline salt of 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole optionally together with an alkaline reacting compound; and an enteric coating, between which and the alkaline reacting core the subcoating is placed, which core material is in the form of small beads or tablets.

The object of the present invention is thus an enteric coated dosage form of acid labile compounds with the general formula I defined above except the compound omeprazole, 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole. Another compound, which may be enteric coated according to the invention is 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole. The new preparations are resistant to dissolution in acid media, dissolve rapidly in neutral to alkaline media and have a good stability during long-term storage. The new dosage form is characterized in the following way. Cores containing the acid labile compound mixed with alkaline compounds or an alkaline salt of the acid labile compound optionally mixed with an alkaline compound are coated with two or more layers, whereby the first layer/layers is/are soluble in water or rapidly disintegrating in water and consist(s) of non-acidic, otherwise inert pharmaceutically acceptable substances. This/these first layer/layers separates/separate the alkaline core material from the outer layer, which is an enteric coating. The final, enteric coated dosage form is treated in a suitable way to reduce the water content to a very low level in order to obtain a good stability with virtually no discolouration of the dosage form during long-term storage.

As examples of compounds especially suitable for the pharmaceutical dosage form according to the invention the compounds listed in Table 1 can be mentioned.

The half-life of degradation of the compounds 1-6 in Table 1 in water solution at pH-values less than four is in most cases shorter than ten minutes. Also at neutral pH-values the degradation reaction proceeds rapidly, e.g. at pH=7 the half-life of degradation is between 10 minutes and 65 hours while at higher pH-values the stability in solution for most compounds is much better. The stability profile is similar in solid phase. The degradation is catalyzed by acid reacting substances. The acid labile compounds are stabilized in mixtures with alkaline reacting substances.

From what is said about the stability properties of the acid labile compounds listed above it is obvious that an oral dosage form of the said compounds must be protected from contact with the acid reacting gastric juice in order to reach the small intestine without degradation.

55

Cores

The acid labile compound is mixed with inert, preferably water soluble, conventional pharmaceutical constituents to obtain the preferred concentration of the active compound in the final mixture and with an alkaline reacting, otherwise

inert, pharmaceutically acceptable substance (or substances), which creates a "micro-pH" around each particle of active compound of not less than pH=7, preferably not less than pH=8, when water is adsorbed to the particles of the mixture or when water is added in small amounts to the mixture. Such substances can be chosen among substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as A1₂O₃·6MgO·CO₂·12H₂O, (Mg₆A1₂(OH)₁₆CO₃·4H₂O), MgO·A1₂O₃·2SiO₂·nH₂O or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane or other similar, pharmaceutically acceptable pH-buffering substances. The stabilizing, high pH-value in the powder mixture can also be achieved by using an alkaline reacting salt of the active compound such as the sodium, potassium, magnesium, calcium salts of acid labile compounds, either alone or in combination with a conventional buffering substance as previously described.

The powder mixture is then formulated into small beads i.e. pellets, or tablets, by conventional pharmaceutical procedures. The pellets or tablets are used as cores for further processing.

15 Separating layer

The alkaline reacting cores containing an acid labile compound must be separated from the enteric coating polymer(s) containing free carboxyl groups, which otherwise causes degradation/discolouration of the acid labile compound during the coating process or during storage. The subcoating layer, (the separating layer), also serves as a pH-buffering zone in which hydrogen ions diffusing from the outside in towards the alkaline core towards the surface of the coated particles. The pH-buffering properties of the separating layer can be further strengthened by introducing in the layer substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance A1₂O₃·6MgO·CO₂·12H₂O, (Mg₆A1₂(OH)₁₆CO₃·4H₂O), MgO·A1₂O₃·2SiO₂·nH₂O, wherein n not is an integer and less than 2 or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, citric or other suitable, weak, inorganic or organic acids.

The separating layer consists of one or more water soluble inert layer, optionally containing pH-buffering compounds.

The separating layer(s) can be applied to the cores - pellets or tablets - by conventional coating procedures in a suitable coating pan or in a fluidized bed apparatus using water and/or conventional organic solvents for the coating solution. The material for the separating layer is chosen among the pharmaceutically acceptable, water soluble, inert compounds or polymers used for film-coating applications such as, for instance, sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, hydroxypropyl cellulose, hydroxymethyl cellulose or hydroxypropyl methylcellulose. The thickness of the separating layer is not less than 2 µm, for small spherical pellets preferably not less than 4 µm, for tablets preferably not less than 10 µm.

In the case of tablets another method to apply the coating can be performed by the drycoating technique. First a tablet containing the acid labile compound is compressed as described above. Around this tablet a layer is compressed using a suitable tableting machine. The outer, separating layer, consists of pharmaceutically acceptable, in water soluble or in water rapidly disintegrating tablet excipients. The separating layer has a thickness of not less than 1 mm. Ordinary plasticizers, colorants, pigments, titanium dioxide, talc and other additives may also be included into the separating layer.

The enteric layer coating layer is applied on to the subcoated cores by conventional coating techniques such as, for instance, pan coating or fluidized bed coating using solutions of polymers in water and/or suitable organic solvents or by using latex suspensions of said polymers. As enteric coating polymers can be used, for example, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl esters such as, for instance, compounds known under the trade name Eudragit® L 12,5 or Eudragit® L 100 (Röhm Pharma), or similar compounds used to obtain enteric coatings.

The enteric coating can also be applied using water-based polymer dispersions, e.g. Aquateric® (FMC Corporation), Eudragit® L100-55 (Röhm Pharma), Coating CE 5142 (BASF). The enteric coating layer can optionally contain a pharmaceutically acceptable plasticizer such as, for instance, cetanol, triacetin, citric acid esters such as, for instance, those known under the trade name Citroflex® (Pfizer), phthalic acid esters, dibutyl succinate or similar plasticizers.

The amount of plasticizer is usually optimized for each enteric coating polymer(s) and is usually in the range of 1-20% of the enteric coating polymer(s). Dispersants such as talc, colourants and pigments may also be included into the enteric coating layer.

Thus, the special preparation according to the invention consists of cores containing the acid labile compound mixed with an alkaline reacting compound or cores containing an alkaline salt of the acid labile compound optionally mixed with an alkaline reacting compound. The cores suspended in water forms a solution or a suspension which has a pH, which is higher than that of a solution in which the polymer used for enteric coating is just soluble. The cores are coated with a water soluble or in water rapidly disintegrating coating, optionally containing a pH-buffering substance, which separates the alkaline cores from the enteric coating. Without this separating layer the resistance towards gastric juice

would be too short and the storage stability of the dosage form would be unacceptably short. The sub-coated dosage form is finally coated with an enteric coating rendering the dosage form insoluble in acid media, but rapidly disintegrating/dissolving in neutral to alkaline media such as, for instance, the liquids present in the proximal part of the small intestine, the site where dissolution is wanted.

5 Final dosage form

The final dosage form is either an enteric coated tablet or capsule or in the case of enteric coated pellets, pellets dispensed in hard gelatin capsules or sachets or pellets formulated into tablets. It is essential for the long term stability 10 during storage that the water content of the final dosage form containing acid labile compound (enteric coated tablets, capsules or pellets) is kept low, preferably not exceeding 1.5 % by weight.

A process for the manufacture of the oral dosage form represents a further aspect of the invention. After the forming 15 of the cores the cores are first coated with the separating layer and then with the enteric coating layer. The coating is carried out as described above.

15 The preparation according to the invention is especially advantageous in reducing gastric acid secretion and/or providing a gastrointestinal cytoprotective effect. It is administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general the dosage will be in the range of 1 to 400 mg per day of active substance. 20 A method for the treatment of such conditions using the novel oral dosage form represents a further aspect of the invention.

The invention is described in detail in the following examples:

EXAMPLES

25 Examples 1-3 exemplify the invention.

Example 1

Uncoated pellets

35	I	<table> <tr> <td>Lactose powder</td><td>253 g</td></tr> <tr> <td>Lactose anhydrous</td><td>167 g</td></tr> <tr> <td>Hydroxypropyl cellulose</td><td>25 g</td></tr> </table>	Lactose powder	253 g	Lactose anhydrous	167 g	Hydroxypropyl cellulose	25 g				
Lactose powder	253 g											
Lactose anhydrous	167 g											
Hydroxypropyl cellulose	25 g											
40	II	<table> <tr> <td>Compound 1, Table 1</td><td>50 g</td></tr> <tr> <td>Sodium lauryl sulphate</td><td>5 g</td></tr> <tr> <td>Disodium hydrogen phosphate</td><td>1.5g</td></tr> <tr> <td>Sodium dihydrogen phosphate</td><td>0.1g</td></tr> <tr> <td>Distilled water</td><td>125 g</td></tr> </table>	Compound 1, Table 1	50 g	Sodium lauryl sulphate	5 g	Disodium hydrogen phosphate	1.5g	Sodium dihydrogen phosphate	0.1g	Distilled water	125 g
Compound 1, Table 1	50 g											
Sodium lauryl sulphate	5 g											
Disodium hydrogen phosphate	1.5g											
Sodium dihydrogen phosphate	0.1g											
Distilled water	125 g											
45												
50												

The dry ingredients (I) were premixed in a mixer. Addition of a granulation liquid (II) containing the suspended active compound was made and the mass was wet-mixed to a proper consistency. The wet mass was pressed through an extruder and spheronized to pellets. The pellets were dried and classified into suitable particle size ranges.

Subcoated pellets

5

		Uncoated pellets	500	g
10	III	{ Hydroxypropyl methyl-		
		cellulose	20	g
		{ Distilled water	400	g

15

The polymer solution (III) was sprayed onto the uncoated pellets in a fluidized bed apparatus. The spray guns were placed above the fluidized bed.

20 Enteric coated pellets

25

		Subcoated pellets	500	g
30	IV	{ Hydroxypropyl methylcellulose		
		phthalate	57	g
		{ Cetyl alcohol	3	g
		Acetone	540	g
		Ethanol	231	g

35

The polymer solution (IV) was sprayed on the subcoated pellets in a fluidized bed apparatus with spray guns placed above the bed. After drying to a water content of 0.5 % the enteric coated pellets were classified and filled into hard gelatin capsules in an amount of 284 mg, corresponding to 25 mg of active compound 1. 30 capsules were packed in tight containers together with a desiccant.

40 Example 2

45 Formulation with the sodium salt of compound 2 according to Table 1.

50

55

Uncoated pellets

5

10

	I	Compound 2, Table 1 sodium salt	339	g
		Mannitol powder	2 422	g
		Lactose anhydrous	120	g
		Hydroxypropyl cellulose	90	g
		Microcrystalline cellulose	60	g

	II	Sodium lauryl sulphate	7	g
		Distilled water	650	g

20

The preparation was made as described in Example 1 with the exception that the sodium salt of compound 2 was added together with the other ingredients in mixture 1.

25

Subcoated pellets

30

35

	III	Uncoated pellets	500	g
		Hydroxypropyl methylcellulose	20	g
		Aluminium hydroxide/magnesium		
		carbonate	4	g

	IV	Pellets subcoated with III	500	g
		Hydroxypropyl methylcellulose	20	g
		Distilled water	400	g

40

45

The two subcoat layers, III and IV, were applied to the uncoated pellets in a fluidized bed apparatus in consecutive order as previously described.

55

Enteric coated pellets

5

10

15

	Subcoated pellets	500	g
10	Hydroxypropyl methylcellulose		
V	phthalate	57	g
	Cetyl alcohol	3	g
	Acetone	540	g
	Ethanol	231	g

The preparation of enteric coated pellets was performed as described in Example 1.

20 Example 3

Formulation with compound 6, according to Table 1. This example gives the composition of one unit dose according to the invention.

25 Tablet core

30

35

40

Compound 6, Table 1	15 mg
Lactose	119 mg
Hydroxypropyl cellulose (low substitution)	5 mg
Hydroxypropyl cellulose	1 mg
Talc	5 mg
Mg(OH) ₂	15 mg
TOTAL	160 mg

Tablet cores having the composition above and each weighing 160 mg were first made by known techniques.

45

Separating layer (inner)

50

55

Hydroxypropyl cellulose	2 mg
Synthetic hydrotalcite [Al ₂ O ₃ · 6MgO · CO ₂ · 12H ₂ O]	0.3 mg

Separating layer (outer)

5

Hydroxypropyl cellulose	2 mg
-------------------------	------

10

The two separating layers were applied to the cores by known coating techniques.

Enteric coating layer

15

20

Hydroxypropyl methylcellulose phthalate	7 mg
Cetyl alcohol	0.5 mg

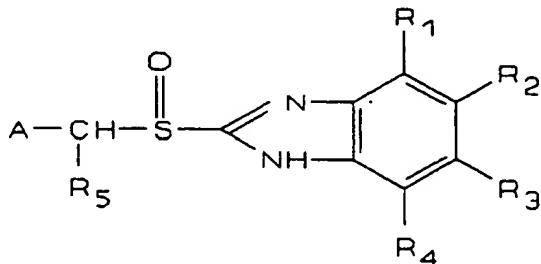
The enteric coating solution was sprayed on the cores coated by the two separating layers by known enteric coating techniques.

Claims

30 1. The use of a subcoating which is comprised of one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, film-forming compounds, optionally containing pH-buffering, alkaline compounds, in order to obtain stability to discolouration in an oral pharmaceutical formulation containing as the active ingredient (i) an acid labile compound of the general formula I

35

40



45

wherein A is an optionally substituted heterocyclic group, R1, R2, R3 and R4 are the same or different and are hydrogen, lower alkyl, lower alkoxy, -CF₃,

50



55

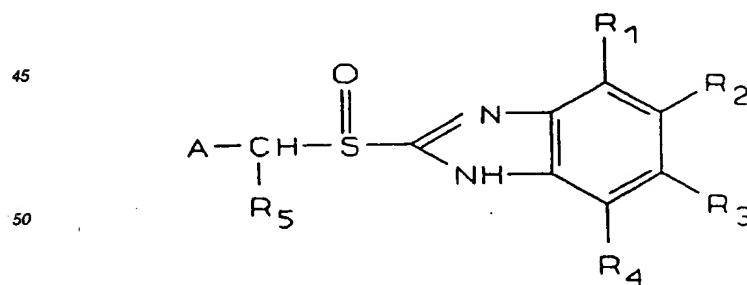
alkyl or halogen and R5 is H or a lower alkyl group wherein "lower" denotes 1-6 carbon atoms, except the compound omeprazole (5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole), together with an alkaline reacting compound, or 2-[(2-dimethylamino-benzyl)sulfinyl]-benzimidazole together with an alkaline

reacting compound, or (ii) an alkaline salt of a compound of formula I optionally together with an alkaline reacting compound, or an alkaline salt of 2-[(2-dimethylamino-benzyl)sulfinyl]-benzimidazole optionally together with an alkaline reacting compound; and an enteric coating, between which and the alkaline reacting core the subcoating is placed, which core material is in the form of small beads or tablets.

- 5 2. The use according to claim 1 wherein the subcoating comprises hydroxypropyl methylcellulose, hydroxypropyl cellulose or polyvinylpyrrolidone.
- 10 3. The use according to claim 1 wherein the subcoating comprises two or more sub-layers and where the inner layer comprises one or more of magnesium oxide, magnesium hydroxide or composite substance $\text{Al}_2\text{O}_3.6\text{MgO}_2\text{O}$ or $\text{MgO}.\text{Al}_2\text{O}_3.2\text{SiO}_2.\text{nH}_2\text{O}$, wherein n is an integer and less than two.
- 15 4. The use according to claim 1 wherein the alkaline core comprises the acid labile compound and pH-buffering alkaline compound rendering to the microenvironment of the acid labile compound a pH of 7-12.
- 20 5. The use according to claim 4 wherein the alkaline compound comprises one or more of magnesium oxide, hydroxide or carbonate, aluminium hydroxide, aluminium, calcium, sodium or potassium carbonate, phosphate or citrate, the composite aluminium/magnesium compounds $\text{Al}_2\text{O}_3.6\text{MgO}.\text{CO}_2.12\text{H}_2\text{O}$ or $\text{MgO}.\text{Al}_2\text{O}_3.2\text{SiO}_2.\text{nH}_2\text{O}$, wherein n is not an integer and less than two.
- 25 6. The use according to claim 1 wherein the alkaline core comprises an alkaline salt of the acid labile compound such as the sodium, potassium, magnesium, calcium or ammonium salt.
- 25 7. The use according to claim 5 wherein the alkaline core comprises an alkaline salt of the acid labile compound mixed with an inert, alkaline compound.
- 30 8. The use according to claim 1 wherein the enteric coating comprises hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl ester or polyvinyl acetate phthalate, optionally containing a plasticizer.
- 30 9. The use according to claim 1 wherein the water content of the final dosage form containing the acid labile compound does not exceed 1.5 % by weight.

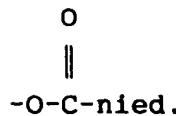
Patentansprüche

- 35 1. Verwendung eines Grundüberzugs, der eine oder mehrere inert reagierende Grundüberzugsschichten enthält, umfassend Tablettenexzipienten, die löslich sind oder in Wasser rasch desintegrieren, oder polymere, wasserlösliche Filmbildner-Verbindungen, gegebenenfalls enthaltend alkalische pH-Puffer-Verbindungen, um eine Stabilität gegenüber einer Verfärbung in einer oralen pharmazeutischen Formulierung zu erhalten, die als aktiven Bestandteil enthält: i) eine säurelabile Verbindung der allgemeinen Formel (I)



55 worin A eine gegebenenfalls substituierte heterocyclische Gruppe bedeutet, R¹, R², R³ und R⁴ gleich oder verschieden sind und Wasserstoff, nied. Alkyl, nied. Alkoxy, -CF₃.

5



Alkyl oder Halogen darstellen, und R⁵ H oder eine nied.Alkyl-Gruppe ist, wobei "nied." 1 bis 6 Kohlenstoffatome bedeutet, ausgenommen die Verbindung Omeprazol (5-Methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazol), zusammen mit einer alkalisch reagierenden Verbindung, oder 2-[(2-Dimethylaminobenzyl)-sulfinyl]-benzimidazol, zusammen mit einer alkalisch reagierenden Verbindung, oder (ii) ein alkalisches Salz einer Verbindung der Formel (I), gegebenenfalls zusammen mit einer alkalisch reagierenden Verbindung, oder ein alkalisches Salz von 2-[(2-Dimethylaminobenzyl)-sulfinyl]-benzimidazol, gegebenenfalls zusammen mit einer alkalisch reagierenden Verbindung; und einen enterischen Überzug, zwischen welchem und dem alkalisch reagierenden Kern der Grundüberzug angeordnet ist, welches Kernmaterial in Form kleiner Kugelchen oder Tabletten vorliegt.

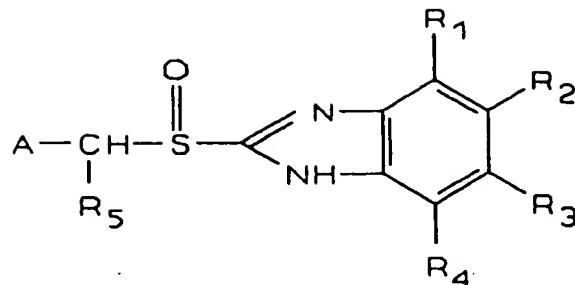
2. Verwendung nach Anspruch 1, wobei der Grundüberzug Hydroxypropylmethylecellulose, Hydroxypropylcellulose oder Polyvinylpyrrolidon umfaßt.
- 20 3. Verwendung nach Anspruch 1, wobei der Grundüberzug zwei oder mehrere Grundsichten umfaßt, und wobei die innere Schicht eines oder mehrere von Magnesiumoxid, Magnesiumhydroxid oder Verbundsubstanz Al₂O₃.6MgO₂O oder MgO.Al₂O₃.2SiO₂.nH₂O, worin n eine ganze Zahl und weniger als 2 ist, umfaßt.
- 25 4. Verwendung nach Anspruch 1, wobei der alkalische Kern die säurelabile Verbindung und alkalische pH-Puffer-Verbindung umfaßt, die der Mikroumgebung der säurelabilen Verbindung einen pH von 7 bis 12 verleiht.
5. Verwendung nach Anspruch 4, wobei die alkalische Verbindung eines oder mehrere von Magnesiumoxid, -hydroxid oder -carbonat, Aluminiumhydroxid, Aluminium-, Calcium-, Natrium- oder Kaliumcarbonat, -phosphat oder -citrat, den zusammengesetzten Aluminium/Magnesium-Verbindungen Al₂O₃.6MgO.CO₂.12H₂O oder MgO.Al₂O₃.2SiO₂.nH₂O, worin n keine ganze Zahl und weniger als 2 ist, umfaßt.
- 30 6. Verwendung nach Anspruch 1, wobei der alkalische Kern ein alkalisches Salz der säurelabilen Verbindung, wie das Natrium-, Kalium-, Magnesium-, Calcium- oder Ammoniumsalz, umfaßt.
- 35 7. Verwendung nach Anspruch 5, wobei der alkalische Kern ein alkalisches Salz der säurelabilen Verbindung, gemischt mit einer inerten alkalischen Verbindung, umfaßt.
8. Verwendung nach Anspruch 1, wobei der enterische Überzug Hydroxypropylmethylecellulosephthalat, Celluloseacetatphthalat, co-polymerisierten Methacrylsäure/Methacrylsäuremethylester oder Polyvinylacetatphthalat, gegebenenfalls enthaltend einen Weichmacher, umfaßt.
- 40 9. Verwendung nach Anspruch 1, wobei der Wassergehalt der die säurelabile Verbindung enthaltenden End-Dosierungsform 1,5 Masse-% nicht überschreitet.

45 Revendications

1. Utilisation d'un sous-revêtement qui est constitué d'une ou de plusieurs couches de sous-revêtement, ne réagissant pas, comprenant des excipients de comprimés qui sont solubles ou se désintègrent rapidement dans l'eau, ou des composés polymères filmogènes solubles dans l'eau, contenant facultativement des composés alcalins tampons de pH, afin d'obtenir de la stabilité à la décoloration dans une formulation pharmaceutique orale contenant comme ingrédient actif (i) un composé instable en milieu acide de formule générale I

5

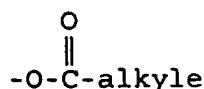
10



15

dans laquelle A est un groupe hétérocyclique facultativement substitué, R₁, R₂, R₃ et R₄ sont identiques ou différents et sont l'hydrogène, un alkyle inférieur, un alcoxy inférieur, -CF₃,

20



25

inférieur ou un halogène et R₅ est H ou un groupe alkyle inférieur, où "inférieur" indique 1 à 6 atomes de carbone, à l'exception du composé oméprazole (5-méthoxy-2-[(4-méthoxy-3,5-diméthyl-2-pyridinyl)méthyl]sulfinyl]-1H-benzimidazole), avec un composé à réaction alcaline, ou le 2-[(2-diméthylaminobenzyl)sulfinyl]benzimidazole avec un composé à réaction alcaline, ou (ii) un sel alcalin d'un composé de formule I facultativement avec un composé à réaction alcaline, ou un sel alcalin du 2-[(2-diméthylaminobenzyl)sulfinyl]benzimidazole facultativement avec un composé à réaction alcaline; et un enrobage entérique, le sous-revêtement étant placé entre cet enrobage et le noyau à réaction alcaline, la substance du noyau étant sous la forme de petits grains ou comprimés.

30

35

40

45

50

55

2. Utilisation conforme à la revendication 1, dans laquelle le sous-revêtement comprend de l'hydroxypropylméthylcellulose, de l'hydroxypropylcellulose ou de la polyvinylpyrrolidone.
3. Utilisation conforme à la revendication 1, dans laquelle le sous-revêtement comprend deux ou plus de deux sous-couches et dans laquelle la couche interne comprend une ou plusieurs des substances: oxyde de magnésium, hydroxyde de magnésium ou substance composite Al₂O₃ · 6MgO₂O ou MgO · Al₂O₃ · 2SiO₂ · nH₂O, où n n'est pas entier et inférieur à 2.
4. Utilisation conforme à la revendication 1, dans laquelle le noyau alcalin comprend le composé instable en milieu acide et le composé alcalin à tampon de pH conférant au microenvironnement du composé instable en milieu acide un pH de 7 à 12.
5. Utilisation conforme à la revendication 4, dans laquelle le composé alcalin comprend une ou plusieurs des substances: oxyde, hydroxyde ou carbonate de magnésium, hydroxyde d'aluminium, carbonate, phosphate ou citrate d'aluminium, de calcium, de sodium ou de potassium, composés composites d'aluminium/magnésium Al₂O₃ · 6MgO · CO₂ · 12H₂O ou MgO · Al₂O₃ · SiO₂ · nH₂O, où n n'est pas entier et inférieur à 2.
6. Utilisation conforme à la revendication 1, dans laquelle le noyau alcalin comprend un sel alcalin du composé instable en milieu acide tel que le sel de sodium, de potassium, de magnésium, de calcium ou d'ammonium.
7. Utilisation conforme à la revendication 5, dans laquelle le noyau alcalin comprend un sel alcalin du composé instable en milieu acide mélangé avec un composé alcalin, inerte.
8. Utilisation conforme à la revendication 1, dans laquelle l'enrobage entérique comprend du phtalate d'hydroxypropylméthylcellulose, de l'acétate phtalate de cellulose, du copolymère acide méthacrylique/ester méthylique de l'acide méthacrylique ou de l'acétate phtalate de polyvinyle, contenant facultativement un plastifiant.

9. Utilisation conforme à la revendication 1, dans laquelle la teneur en eau de la formulation finale contenant le composé instable en milieu acide ne dépasse pas 1,5% en poids.

5

10

15

20

25

30

35

40

45

50

55